Not for publication or presentation

MINUTES AND OVERVIEW PLAN
CIBMTR WORKING COMMITTEE FOR ACUTE LEUKEMIA
San Antonio, TX
Wednesday, February 21, 2024, 1:00 – 3:00 PM CT

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1. **Introduction**
2. **Accrual summary**

   The accrual summary was not presented due to time constraints but was made available to attendees as an attachment.
3. **Presentations, published or submitted papers**

   Details regarding presentations and publications were not presented due to time constraints but were made available to attendees as an attachment.
4. **Studies in progress**

   Details regarding the studies in progress were not presented due to time constraints but were made available to attendees as an attachment.
5. **Future/proposed studies**

   Dr. Filippo Milano welcomed the first presenter.

   A. **PROP 2309-12/2310-19/2310-50** Evaluating Outcomes of Allogeneic Hematopoietic Cell Transplantation in Therapy Related Acute Lymphoblastic Leukemia (N Chokr/ R Vasudevan Nampoothiri/ H Murthy/ M Kharfan Dabaja)

Dr. Chokr presented the proposal on behalf of the group. The group hypothesize allogeneic stem cell transplant is associated with durable remissions in patients with therapy related ALL and outcomes are similar to a matched patient cohort with de novo ALL. The group will explore the overall survival as the primary endpoint. The second endpoints include progression, free survival, non-relapse, mortality, cumulative incidence of relapse, cumulative incidence of GVHD. The study also emphasized the importance of examining other variables such as disease status prior to transplant, cytogenetics, lineage, conditioning intensity, HCT comorbidity index, age, and prior malignancies. The current literature is limited by small retrospective studies, small samples. Through CIBMTR, the group believes that we can conduct the largest study to define this high-risk category of patients and evaluate the role of allogenic stem cell transplant in therapy-related ALL. We identified 1400 cases with therapy-related ALL and 1700 patients with de novo ALL in the CIBMTR database.

The proposal was opened for questions and comments from the audience. Dr. Kebriaei suggested we need to account for the difference of HCT-CI score between two groups. A member of audience asked if the team take changes in practice for all transplantation over time into account and made a comment on different therapies within different diseases may have different biologic implications. Another member suggested that the team should do some matching between therapy-related cohort and de novo cohort. Dr. Milano expressed concern about the missing cytogenetics information for therapy-related ALL patients. Another member mentioned we should focus more on understanding transplantation and therapy and do not get too caught up in the comparison.

B. **PROP 2309-21/2310-25** Optimal Donor Selection for older adults undergoing Allo SCT for MDS or AML in the era of PTCY (N Khaire/ N Chokr/ A Gomez Arteaga/ A Law/ M Sorror)

Dr. Khaire presented the proposal on behalf of the group. The group hypothesize that the use of PTCY based GVHD prophylaxis helps bridge the gap between outcomes across donor types. This would allow donor selection to prioritize other variables (e.g. donor age, availability, etc.) over HLA matching alone. It intends to improve patient safety by guiding optimal donor choice and also potentially reduces donor availability as a barrier for transplant by establishing the role of mismatch transplants. The primary outcome is overall survival, with secondary outcomes including disease-free survival, non-relapse mortality, and graft-versus-host disease. The study will compare outcomes between four donor types, including haploid, mismatched, and fully matched, unrelated donors. The primary statistical analysis plan involves comparing transplant outcomes among the four donor types using PTCY, while using cases without PTCY as a reference cohort. The study will include all adults over 65 undergoing first allogenic stem cell transplant for either AML or MDS, with a focus on those over 70 and those with high comorbidity. We identified 12487 eligible cases receiving first allo transplant for AML and MDS.

The proposal was opened for questions and comments. A member of the audience suggested the group should consider lowering the age of cases they included, as the study only had around 200 patients who got PTCY. A member mentioned that there might be considerable overlap between this study and another completed one. A concern was raised because we don't know how unique the dataset is compared to other groups.

C. **PROP 2310-31/2310-33/2310-111/2310-206/2310-266** Real-world experience (RWE) of adult patients receiving CD19-CAR-T cell therapy for B cell Acute Lymphoblastic Leukemia (B-ALL) (K Wudhikarn/ M Perales/ M Abid/ F Cervoni-Curet/ A Mirza/ L Gowda/ N Bejanyan)

Dr. Mirza presented the proposal concept. The group hypothesizes that real-world toxicity and efficacy for adult patients with B-ALL receiving CD19 CART cell is similar and comparable to registration trial data. The group also hypothesizes outcomes of adult patients with B-ALL treated with CD19 CART cell depends on patient characteristics, CART products, or prior therapies and outcomes of adult patients with MDS B-ALL after induction chemotherapy are comparable between those who receive CD19 CART cells versus allo-HCT. The primary aim of the study is to describe the toxicity and efficacy of adult patients with B-ALL as they receive CD 19 CART cells. The group want to explore the toxicity and efficacy data between 2 CART products and how prior therapy impact CART outcomes. We identified 800+ cases receiving CD19 CART therapy during 2017-2023 in CIBMTR database.

The floor was opened for questions and comments from the audience. A member of audience suggested that the group need to look at the activity of CART in patients who had a prior allo-HCT versus who didn't without considering whether allo-HCT is given as consolidation. Another member inquired whether the group is aware of the patients who received CAR-T cells in a clinical trial as opposed to real-world scenarios. A member suggested it would be important to also capture the sequencing of when the blinatumomab was given.

D. **PROP 2310-42** Safety and efficacy of CAR-T cell therapy in relapsed/refractory acute lymphoblastic leukemia with central nervous system involvement
(L Gonzalez Mosquera/ S Farhan)

Dr. Mosquera presented the proposal concept. The study hypothesizes that CART cell therapy can be a safe and effective option in relapsed/refractory acute lymphoblastic leukemia with CNS involvement. The study looks to evaluate progression free survival of CART therapy in relapsed/refractory ALL with central nervous system involvement (CNS). Also, the study aims to evaluate overall survival of CART therapy in relapsed/refractory ALL with CNS involvement and safety of CART therapy in relapsed/refractory ALL with CNS. Besides, the study looks to evaluate the influence of prior therapy lines used in the efficacy of CART: Blinatumomab, inotuzumab, TKIs and allo-HCT. The group believes this study give clinicians real-world data to have certainty of the use of CART therapy in ALL with CNS involvement. We identified 71 patients receiving CART with ALL and CNS2 and CNS3 involvement in CIBMTR database.

The floor was opened for questions and comments from the audience. A concern has been raised about the potential bias present in real-world data, as patients might receive CAR-T therapy despite the likelihood of exclusion in most cases. A member asked if there is a way that the investigator could quantify the amount of diseases patients had in the CNS. Another member suggested the group should look at patients with CSF only versus with parenchymal involvement. Also, on of the chairs suggested the group could consider if the patients got radiation therapy as another variable.

E. **PROP 2310-87/2310-89/2310-116/2310-127/2310-190** Sequencing of chimeric antigen receptor T-cell therapy and allogeneic transplantation in adult patients with B-cell acute lymphoblastic leukemia (D Eng/ H Sibai/ R Mohty/ M Kharfan-Dabaja/ J Wang/ L Metheny/ J Fein/ A Gomez-Arteaga)

Dr. Fein presented the concept. The group hypothesizes that outcomes, including overall survival as well as key toxicities, are affected by the combination and sequencing of allogeneic HCT and CAR-T in adult patients with relapsed/refractory B cell ALL. The study primarily aims to compare overall survival among patients with consolidative allo-HCT after CD19 CART versus observation. Also, it looks to evaluate the overall survival and distinct toxicity profile of CART after prior allo-HCT. The group would like to establish a dedicated data repository for further exploration of therapy sequencing in B-ALL disease subsets. In CIBMTR database, there are total of 509 research-eligible adult patients who have received CART for relapsed/refractory B-ALL.

The floor was opened for questions and comments from the audience. A member asked how the group handle confounders in this study, particularly considering the aggressive nature of allo-HCT treatment and potential reasons for selecting it (patients had MRD detection after CART). Another member asked if the group thought of stratifying by type of product. Also, another member suggested the group should do landmark analysis at a certain time point. There was a raised concern regarding the limited patient count within the study cohort. A member asked if the group exclude patients who had relapse after CART therapy and then received the allo-HCT.

F. **PROP 2310-93** Comparison of FluFTBI and other myeloablative conditioning regimens for haploidentical and mismatched unrelated hematopoietic cell transplant with post-transplant cyclophosphamide in patients with acute leukemia (S Arslan/ M Al Malki)

Dr. Arslan presented the concept. The group hypothesizes that in patients with acute leukemia, outcomes of haploidentical and MMUD hematopoietic cell transplant with post-transplant cyclophosphamide (PTCy) are better with conditioning therapy comprising fludarabine with FTBI as compared to other conditioning therapies used as myeloablative conditioning (MAC). The study aims to evaluate HCT outcomes in patients with AML and ALL who underwent haploHCT or MMUD HCT with PTCy with MAC consisting of either FluTBI or other MAC and were registered CIBMTR. The overall survival will be compared between the two groups of MAC as the primary endpoint. The study will also compare non-relapse-mortality (NRM), relapse rate, progression-free-survival (PFS) and leukemia-free-survival (LFS). In CIBMTR database, there are total of 3714 research-eligible patients with AML or ALL who underwent MAC and PTCy and haplo, MMUD6/8 or MMUD7/8 HCT during 2008-2022.

The floor was opened for questions and comments from the audience. A member asked how many cases the group have for this study and suggested the study could include more. Another member asked what the proportion of myeloablative the FluTBI were. A member suggested that the group should exclude patients prior to 2017 and also mentioned there might be a confounder as the group combined ALL and AML, since AML patients might be older and TBI usage might be low. Furthermore, another member expressed concern that the group might overlook some potentially valuable therapy combinations by consolidating everything together. An audience asked if the group would like to consider include FluMel conditioning regimen.

G. **PROP 2310-97/2310-186** Transplant Outcomes Based on Intensity of Induction in Adult Patients with Ph+ ALL (A Ali/ A Chergui/ A Pelcovits)

Dr. Chergui presented the concept. The group hypothesize that adult patients with Ph+ ALL receiving low intensity TKI induction regimens prior to allo-HCT will have non-inferior or better survival outcomes after transplant with fewer treatment related complications than patients receiving TKIs in combination with multi-agent chemotherapy (high intensity) induction. The overall survival of patients would be the primary outcome and the secondary outcomes include TRM, incidence of cGVHD and aGVHD, leukemia free survival and functional status post-transplant. The study will help guide clinical decision making for initial choice of induction therapy prior to allo-HCT and will provide supporting evidence, albeit retrospective, on choice of less toxic induction strategies. In CIBMTR database, there are total of 1178 research-eligible adult patients who have received chemotherapy treatment prior to allo-HCT between 2008-2020.

The floor was opened for questions and comments from the audience. A member asked how many patients received myeloablative conditioning regimen and how many patients received reduce intensity regimen. A concern was raised that the combination of therapy might not be correct. Another member mentioned that there is a significant confounder because the patients who either do not undergo transplant or fail initial TKI therapy, then have to switch therapies, and may or may not ultimately receive a transplant.

H. **PROP 2310-122/2310-187/2310-199** Impact of prior novel therapies on post-transplant outcomes in B-ALL (A Sayyed/ I Pasic/ A Chergui/ J Reagan/ M Connor/ N Frey)

Dr. Connor presented the concept. The group has two aims. First, the group wants to determine if receipt of B-cell targeted agents as part of therapy to achieve CR1 is associated with post-HCT survival. They hypothesize that patients who receive B-cell targeted therapies prior to transplant have improved post-transplant relapse-free survival. They also hypothesize that n patients receiving B-cell targeted therapies prior to transplant, there is no difference in relapse-free survival between those who receive RIC versus MAC. The second aim is to assess whether salvage treatment strategy for relapsed/refractory B-ALL patients who achieve CR2+ is associated with durability of remission and survival post-HCT. They hypothesize patients who receive CART19 as part of successful salvage therapy have improved RFS post-HCT compared to those who do not. The group would like to inquire whether more intensive conditioning is necessary in the era of modern B-cell targeted therapy, improve prognostication/risk stratification of patient going to HCT in the setting of evolving frontline therapies and identify salvage/bridging strategies that will improve post-HCT outcomes. In CIBMTR database, there are total of 15028 patients research-eligible adult patients since 2010.

The floor was opened for questions and comments from the audience. A member commented that the selection of conditioning regimen may be more influenced by the presence of minimal residual disease (MRD) rather than the salvage therapies received. A concern was raised by one of chairs that some therapy may not be strong enough to put patients into remission, thus the dataset might not be suitable for the second aims.

I. **PROP 2310-146** The role of HLA class II mismatched HCT in patients with high-risk acute leukemia (R Mehta/ A Ruggeri)

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Dr. Mehta presented the proposal concept. The group hypothesized that among patients with 'high-risk' acute leukemia, patients with HLA class II (-DRB1 or -DPB1) mismatched HCT would have a lower risk of relapse than those with HLA class II matched HCT. The study defines individuals at high risk based on specific criteria: primary induction failure, active disease at the time of transplant, positive minimal residual disease (MRD) status, or presence of high-risk features as outlined by the European Leukemia Net (ELN) classification, even in cases of complete remission. Furthermore, in acute lymphoblastic leukemia (ALL) patients, any instance of hypodiploidy would be categorized as high risk. If relapse is indeed lower, and no significant impact on NRM, findings could be potentially practice changing.

The floor was opened for questions and comments from the floor. A member suggested the group could categorize AML and high risk MDS together as a similar biological entity, while treating ALL as a separate group. Another member asked the group's approach to handling DQ and how the group handle dual mismatches in DPB1 and DRB1.

Proposed studies; not accepted for consideration at this time.

J. **PROP 2310-04** Impact of depth of response in outcomes on patient with ALL in remission undergoing allogeneic stem cell transplantation.
K. **PROP 2310-10** Outcomes of allogeneic hematopoietic cell transplantation in relapsed/ refractory acute myeloid leukemia with active disease.
L. **PROP 2310-15** Donor and Conditioning Choice for Patients with a High Comorbidity Age Index Score without a Matched Sibling Donor.
M. **PROP 2310-17** Outcomes and Predictors of outcomes after allogeneic hematopoietic stem cell transplantation in adult patients with therapy-related hematological malignancies developing after multiple myeloma.
N. **PROP 2310-34** Predictive factors of response to subsequent salvage treatments for post-transplant relapse in patients with myeloid neoplasm who relapsed following allogeneic hematopoietic cell transplant.
O. **PROP 2310-39** Stability of FLT3 mutation at relapse post allogenic transplant in FLT3 ITD mutation positive AML in the era of FLT3 inhibitors and its impact on prognosis.
P. **PROP 2310-40** Optimization of Graft-versus-Acute Myeloid Leukemia Effect for Human Leukocyte Antigen-Matched Hematopoietic Stem Cell Transplantation in Patients Receiving Post-Transplant Cyclophosphamide.
Q. **PROP 2310-82** Impact of Hypomethylating agents Consolidation post Allogeneic Hematopoietic cell Transplantation among AML and MDS patients.
R. **PROP 2310-86** Use of FLT-3 inhibition in the peri-transplant period and its effect on transplant-related outcomes in patients with FLT-3 ITD positive Acute Myeloid Leukemia in CR1 in the CIBMTR database.
S. **PROP 2310-98** Outcomes of allogeneic hematopoietic stem cell transplant in patients with Ph+ve Acute Myeloid Leukemia.
T. **PROP 2310-104** Timed sequential busulfan to overcome MRD positivity and decrease the risk of leukemia relapse.
U. **PROP 2310-105** Impact of salvage therapy on outcomes post allogeneic transplantation for patients with relapsed/refractory B-cell acute lymphoblastic leukemia.
V. **PROP 2310-114** Characteristics and Post-Transplant Outcomes of Patients with Core-Binding Factor Acute Myeloid Leukemia.
W. **PROP 2310-115** Validation of the Transplant Conditioning Intensity (TCI) Score for Allogeneic Hematopoietic Cell Transplantation (alloHCT) in Acute Myeloid Leukemia (AML) Patients Receiving GVHD Prophylaxis with Post-Transplantation Cyclophosphamide (PTCy).

X. **PROP 2310-117** Outcomes of T-Cell Depleted Stem Cell Transplantation in Acute Myeloid Leukemia and High-Risk Myelodysplastic Syndrome.

Y. **PROP 2310-118** Chimeric antigen receptor (CAR) T-cell therapy versus Donor Lymphocyte Infusions (DLI) following Allogeneic Hematopoietic Stem Cell Transplantation in Acute Lymphoblastic Leukemia and Non-Hodgkin Lymphoma.

Z. **PROP 2310-124** Choice of therapy for Patients with AML Relapsing after Allogeneic Transplant in the Modern Era.

AA. **PROP 2310-132** Evaluating survival outcomes of allogeneic hematopoietic stem cell transplantation in patients with isolated myeloid sarcoma.

BB. **PROP 2310-154** Impact of Early/ Late donor chimerism on outcomes in Acute Myeloid Leukemia/Myelodysplastic syndrome after reduced-intensity conditioning hematopoietic cell transplantation with matched sibling or matched unrelated donor transplant.

CC. **PROP 2310-158** Development of prognostic pre-transplant risk score for patients undergoing allogeneic HCT for acute leukemia transplanted in complete remission.

DD. **PROP 2310-168** Donor Lymphocyte infusion vs. second allogeneic hematopoietic cell transplantation for relapse after transplantation for AML/MDS- A CIBMTR analysis.

EE. **PROP 2310-174** Comparing Overall Survival in Patients Undergoing Allogenic Transplant with Extramedullary AML in Comparison to those with Intramedullary AML.

FF. **PROP 2310-176** Donor lymphocyte Infusions with Hypomethylating agents in prophylaxis or treatment of relapse post Allogeneic Hematopoeitic Cell Transplants in Acute Myeloid Leukemia and Myelodysplastic Syndromes.

GG. **PROP 2310-184** Haploidentical versus mismatched unrelated donor transplant with post-transplant cyclophosphamide in Acute Myeloid Leukemia and High-Risk Myelodysplastic Syndrome.

HH. **PROP 2310-196** A Comparison of Fludarabine with Total Body Irradiation versus Etoposide with Total Body Irradiation as conditioning regimens for patients undergoing Allogeneic Stem Cell Transplantation for Acute Lymphoblastic Leukemia in First or Second Complete remission..

II. **PROP 2310-202** Impact of Clonal Evolution in Post-Transplantation Relapsed Myeloid Neoplasms.

JJ. **PROP 2310-203** Prognostic significance of the AML European Leukemia Net 2022 risk stratification for patients undergoing allogeneic stem cell transplantation with subgroup analysis based on age and race.

KK. **PROP 2310-224** Outcome of patients with Acute Myeloid leukemia (AML) after allogeneic hematopoietic cell (HCT) transplantation using novel International Consensus Classification (ICC) classification 2022 for AML in comparison to patients with AML using WHO classification (2016).

LL. **PROP 2310-226** Chimeric antigen receptor T-cell therapy versus Donor Lymphocyte Infusions following Allogeneic Hematopoietic Stem Cell Transplantation in Acute Lymphoblastic Leukemia and Non-Hodgkin Lymphoma.

MM. **PROP 2310-227** Survival after relapse following first allogeneic transplant for patients with AML and MDS in the modern era.

NN. **PROP 2310-229** Impact of Clonal Evolution in Post-Transplantation Relapsed Myeloid Neoplasms.

OO. **PROP 2310-247** The impact of obesity and body weight on outcomes in patients with lymphoid malignancies treated with CAR-T therapy.

PP. **PROP 2310-249** Characterizing differences in clinical outcomes of commercial CAR T-cell therapy for relapsed/refractory ALL and LBCL large B-cell lymphoma based on gender.

QQ. **PROP 2310-268** Impact of mixed donor chimerism and donor lymphocyte infusions on future relapse in the post-transplant cyclophosphamide-based graft versus host disease (GVHD) prophylaxis setting.

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Working Committee Overview Plan for 2024-2025		
Study number and title	**Current status**	**Chairs priority**
LK19-02: Evolving significance of Philadelphia chromosome status on acute lymphoblastic leukemia prognosis in the TKI era	Manuscript Preparation	1
LK20-01: Acute myeloid leukemia with chromosome 17 abnormalities with or without TP53 abnormalities and outcomes after hematopoietic stem cell transplantation	Data File Preparation	1
LK20-02: Outcomes of allogeneic hematopoietic cell transplantation among germline RUNX1 mutation carriers with acute myeloid leukemia	Manuscript Preparation	1
LK20-03: Evaluating outcomes of allogeneic hematopoietic cell transplantation in T-cell acute lymphoblastic leukemia	Data File Preparation	1
LK21-01: Impact of measurable residual disease status on outcomes of acute myeloid leukemia and patients 18-65 years old in first complete remission undergoing allogeneic hematopoietic cell transplantation	Manuscript Preparation	2
LK22-01: Intensive induction chemotherapy vs. hypomethylating agent therapy for older AML patients undergoing allogeneic hematopoietic cell transplantation	Data File Preparation	3
LK23-01: The impact of allogeneic stem cell transplantation on acute myeloid leukemia and myelodysplastic syndrome with chromosome 3 abnormalities.	Protocol Development	3
LK23-02: Prognostic impact of cytogenetic and molecular risk classification in AML after hematopoietic stem cell transplant in adolescents and young adults.	Protocol Development	2
LK23-03: Impact of donor source in second allogeneic hematopoietic cell transplant in patients with acute leukemia/MDS who relapsed after prior allograft during the current era (2014-2020)	Protocol Development	2
LK24-01: a. Sequencing of chimeric antigen receptor T-cell therapy and allogeneic transplantation in adult patients with B-cell acute lymphoblastic leukemia. b. Safety and efficacy of CAR-T cell therapy in relapsed/refractory acute lymphoblastic leukemia with central nervous system involvement. c. Real-world experience (RWE) of adult patients receiving CD19-CAR-T cell therapy for B cell Acute Lymphoblastic Leukemia (B-ALL).	Protocol Development	3